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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,818	04/26/2001	Anthony Steven Weiss	GHC11USA	8602

270 7590 08/19/2005

HOWSON AND HOWSON
ONE SPRING HOUSE CORPORATION CENTER
BOX 457
321 NORRISTOWN ROAD
SPRING HOUSE, PA 19477

EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/743,818	WEISS, ANTHONY STEVEN
	Examiner	Art Unit
	Holly Schnizer	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-58,60,61 and 63-89* is/are pending in the application.

4a) Of the above claim(s) *68-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-58,60,61 and 63-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 46-58, 60-61, and 63-89 are pending. Claims 68-89 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 46-58, 60-61, and 63-67 have been considered in this Office Action.

Claim Objections--(Withdrawn)

The objection of Claims 50, 51, and 59 for the recitation of "aa" has been withdrawn in light of the amendment.

Claim Objections--(Maintained)

Claims 60, and 61 are objected to for the recitation of "aa". For clarity, this abbreviation should be written out as "amino acids". Applicants did not address the objection to these claims by amendment or response therefore the objection is maintained.

Rejections Withdrawn

The rejection of Claims 49 and 50-57 under 35 U.S.C. 112, second paragraph for improperly depending from themselves is withdrawn in light of the amendment of Claims 49 and 50.

The rejection of Claims 49-66 under 35 U.S.C. 112, second paragraph as indefinite for the recitation of "capable of" as this is a latent term which implies that there are times that the sub-sequence cannot be digested by the given protease is withdrawn in light of the amendments to Claims 49, 54, 55, 56, 58, and 65.

The rejection of Claims 46-67 are indefinite as to the metes and bounds of "sub-sequence" is withdrawn in light of the amendment.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The present rejection has been modified due to the amendment of the claims. The claims have been amended to recite, "so that the mutated amino acid sequence is not cleaved by the protease". However, the goal of the claimed method is to reduce susceptibility of tropoelastin to proteolysis (by any protease). Thus, the last step of the method is inconsistent and narrower than the goal of the method. Protease susceptibility could not be reduced by merely mutating a serine protease cleavage site or a metalloproteinase cleavage site because the tropoelastin is susceptible to cleavage by many different proteases with different recognition sequences. For example, the Specification indicates that trypsin digestion of tropoelastin was very extensive and, given enough time, resulted in complete degradation (p. 51, lines 1-3). Thus, making a mutation in the serine protease recognition sequence RAAAGLG might reduce susceptibility of tropoelastin to thrombin and kallikrein cleavage *at that site* (it would not reduce overall susceptibility to thrombin and kallikrein cleavage because they recognize more than one sequence as shown in Table 1) but there is no evidence that it would

reduce susceptibility of tropoelastin to trypsin cleavage. Thus, the enablement rejection is maintained for reasons cited in the previous Office Action and herein. The rejection as modified to address the amendments appears below. A response to Applicants arguments follows the rejection.

Rejection:

Claims 46-58, 60-61, and 63-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing the susceptibility of tropoelastin to thrombin, kallikrein, trypsin, plasmin, gelatinase B, or serum by mutating the sequences described in the Specification (see Table I for example), does not reasonably provide enablement for a method for reducing the susceptibility of a tropoelastin to proteolysis by *any* protease comprising mutating *any* sequence in the tropoelastin so that the susceptibility of the tropoelastin to a serine protease or a metalloproteinase is reduced. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation would be required to characterize all of the possible protease cleavage sites in tropoelastin so that the full scope of the claimed method could be practiced with a reasonable expectation of success. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The *nature of the invention* involves the finding of potential cleavage recognition sites in the tropoelastin sequence for thrombin, kallikrein, trypsin, plasmin, gelatinase B, and serum by digesting tropoelastin with each protease and sequencing the resulting peptide fragments.

The *breadth of the claims* is so broad as to encompass reduction of the susceptibility of tropoelastin to cleavage by any protease by mutating any sequence in tropoelastin that results in eliminating the cleavage by a serine protease or a metalloproteinase. Claim 46 (the only independent claim) is not limited as to the size of the sequence to be mutated. Since each tropoelastin is made up of a single amino acid sequence and that sequence as a whole is susceptible to protease cleavage, the phrase "mutating an amino acid sequence of the tropoelastin which is susceptible to cleavage by one or more proteases selected from the group consisting of a serine protease and a metalloproteinase" has been interpreted to encompass the full-length tropoelastin sequence (thus the mutation can be made anywhere on the tropoelastin regardless of how close it is to the actual cleavage site of a particular protease).

The *state of the prior art and relative skill of those in the art* is such that those of skill in the art were aware that serine proteases were involved in the processing of tropoelastase. For example, Mecham et al. (references AY, AZ, and AAR of IDS filed May 24, 2001) describe an enzyme that cleaves tropoelastin with a trypsin like specificity. Hayashi et al. (ref. AW) of IDS filed May 24, 2001) describe a 45 kD

tropoelastin degradation product processed by a metal protease. And, Romero et al. (ref. AAT of IDS filed May 24, 2001) teaches that calcium dependent proteases, kallikrein, trypsin, and elastase are effective in the degradation of tropoelastin but that the major source of proteolytic activity in serum was not clear. There is no teaching or suggestion in the art of mutating protease cleavage sites contained in tropoelastin in order to decrease susceptibility to protease cleavage. In addition, there are innumerable proteases with unique sequence specificities such that any protein can be completely degraded with a combination of non-specific proteases (for example, pronase, a mixture of non-specific proteases from S. griseus is often used to give complete proteolysis; see Voet and Voet, Biochemistry N.Y., John Wiley & Sons, 1990, p. 116.

The Specification provides *guidance and examples* of resulting peptide sequences after tropoelastin digestion with thrombin, kallikrein, trypsin, plasmin, gelatinase B, and serum (see Table I). The Specification does not provide any examples of a specific tropoelastin wherein a protease cleavage is reduced or eliminated by mutation of a protease cleavage site. The Specification and claims do provide guidance as to what specific protease cleavage sequences and which amino acids within those sequences could be mutated. For example, the specification and claims indicate that susceptibility of tropoelastin to thrombin, kallikrein, or serum cleavage could be reduced by mutating the sequence RAAAG at position 515 in the human tropoelastin sequence (see Table I and claims) and more specifically by replacing arginine with alanine. In addition, claim 54 indicates that tropoelastin

susceptibility to thrombin cleavage could be reduced by mutating the amino acid sequence of SEQ ID NOs: 8 or 9 in the tropoelastin sequence. Claim 55 indicates that tropoelastin susceptibility to plasmin can be reduced by mutation of the sequences of SEQ ID NO:11 or 12 in the tropoelastin sequence. Claim 57 indicates that tropoelastin susceptibility to kallikrein cleavage can be reduced by mutation of the sequences of SEQ ID NOs: 9 or 10 within the tropoelastin sequence. Claim 59 indicates that tropoelastin susceptibility to metalloproteinase cleavage can be reduced by mutating the sequence of amino acids 1-5 of SEQ ID NO: 13 or any one of SEQ ID NOs: 45-70 within the tropoelastin sequence. Claim 66 indicates that the susceptibility of tropoelastin to gelatinase A or B cleavage can be reduced by mutating the amino acid sequence of SEQ ID NO: 13 in the tropoelastin sequence. Thus, given the examples summarized in Table I and the guidance in the Specification, these methods involving mutating specific sequence to result in reduced susceptibility to specific protease cleavage are considered enabled.

Given the lack of knowledge about tropoelastin susceptibility to proteases other than those tested in the present Specification and their recognition sites in tropoelastin, it would be highly unpredictable as to what sequences other than those described in the Specification could be mutated to reduce protease susceptibility.

Therefore, for the reasons given above, the quantity of experimentation required to practice the claimed method commensurate in scope with the claims is considered undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant

application but a substantial inventive contribution on the part of a practitioner which would involve the determination of all the proteases that cleave tropoelastin and the cleavage recognition sites in order to reduce the susceptibility of tropoelastin to proteolysis. It is this additional characterization constitutes undue experimentation.

Response to Applicants Arguments:

Applicants contend that there would be no undue experimentation required by a person skilled in the art to carry out the full scope of the method of the invention because the specification provides numerous sequences which may be mutated to reduce susceptibility of tropoelastin to proteolysis by metalloproteinases or serine proteases.

This argument has been considered but is not deemed persuasive. First, while the specification identifies some potential protease cleavage sites in tropoelastin, the specification does not identify all sequences in tropoelastin that are susceptible to protease cleavage. Even for the proteases studied, the Specification admits that not all the plasmin and trypsin-produced peptides were able to be identified unambiguously (see p. 54, lines 26-27 of Specification). Table 1 represents about 11 unique protease recognition sequences (some sequences are repeated because they appear to be recognized by more than one protease), 5 of which are represented in SEQ ID NOs: 8-12. The sequences of SEQ ID NOs: 17-14 are 8 sequences of 8 amino acids representing the single serine protease recognition sequence, wherein each sequence has one or two substitutions of amino acids not required for protease recognition. Likewise, SEQ ID NOs: 45-70 are sequences of 8 amino acids representing a single

metalloproteinase recognition sequence, wherein each sequence has one or two substitutions of amino acids not required for protease recognition. Second, as explained above, mutation of a serine protease or metalloproteinase cleavage site would not reduce the susceptibility of tropoelastin to proteolysis by any protease because it would have the same susceptibility to all proteases that recognize different cleavage sites than the one mutated. For example, kallikrein (a serine protease) appears to cleave at the following sequence: R/SLSPELREGD (see Table 1). However, this sequence is not cleaved by gelatinase B (a metalloproteinase). Therefore, mutating the protease recognition site, RSLSPELREGD, might reduce susceptibility of tropoelastin to kallikrein cleavage (see Table 1) but not to gelatinase B cleavage because gelatinase B would continue to cleave at its own unique protease cleavage sites.

Conclusions

No Claims are allowable.

The prior art of record does not teach or suggest mutating the specific sequences provided in the Specification in order to reduce susceptibility of tropoelastin to cleavage by the corresponding specific proteases.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
August 10, 2005

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER